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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/033,223	12/27/2001	David Botstein	GNE.2930R1C9	7370

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EXAMINER	
SPECTOR, LORRAINE	
ART UNIT	**PAPER NUMBER**
1647	

DATE MAILED: 12/01/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/033,223	BOTSTEIN ET AL.	
	Examiner	Art Unit	
	Lorraine Spector, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 August 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *22-29,32-35 and 37-41* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22-29,33-35 and 37-41* is/are rejected.

7)☒ Claim(s) *32* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Part III: Detailed Office Action

Claims 22-29, 32-35 and 37-41 are pending and under consideration.

The claims are drawn to nucleic acids encoding a protein identified as PRO1800.

Formal Matters:

The new title of the invention is acknowledged.

The information disclosure statement filed 8/12/2004 has not been considered, as it is duplicative of the earlier IDS.

The rejection of claims 22-41 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement regarding the lack of adequate biological deposit is withdrawn in view of claims.

The rejection of claims 22-41 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of applicant's amendments to the specification.

Priority Determination:

The utility for the claimed nucleic acids is based upon Example 16, in which it is shown that the DNA exists in at least 2-fold higher copy amount in 6/9 of tested lung squamous cell carcinoma cell lines. No priority exists for that result in provisional application 60/112851. The earliest disclosure of this result that can be confirmed by the Examiner is in PCT/US99/28634, of which applicants have made of record a copy of the relevant portion. Accordingly, priority is set at 12/1/99.

Objections and Rejections under 35 U.S.C. §112:

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 22-29, 35 and 37-41 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the nucleic acid of SEQ ID NO: 1 or fragments of such that are usable as hybridization probes, does not reasonably provide enablement for degenerate variants of such, which might encode a similar protein, nor for nucleic acids 80, 85, 90, or 95% identical to such, nor which encode a protein 80, 85, 90, or 95% identical to the protein of SEQ ID NO: 1, nor nucleic acids which hybridize to any of the above, any of the aforementioned which are overexpressed in lung or colon tumor. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. This rejection is maintained for reasons of record. Although applicants have amended the claims to indicate that the nucleic acid or protein encoded thereby is found in increased amount in lung or colon tumors, it remains that there is but a single working embodiment, SEQ ID NO: 1, which was so found. The claims represent a mere invitation to experiment to determine other species that might be so associated. The Examiner further notes that the DNA of PRO1800 was only found at increased levels in 5 of 17 tested colon cancer cell lines, and in those, only to a minimal degree, the data indicating an approximate 2-fold increase, which given the minor nature of the increase, taken with the fact that a minority of samples showed such increase, seems to be clearly associated with aneuploidy, and not diagnostic for colon cancer. Note that the previous Office Action clearly indicated enablement only as drawn to *lung*, and not *colon*, cancer.

Applicants traversal of this rejection in the paper filed 8/12/2004 has been fully considered but is not deemed persuasive.

Applicants argue beginning at page 17 of the response that the increased amounts of nucleic acid are predictive of the protein being overexpressed commensurately. This argument has been fully considered but is not deemed persuasive because Applicants arguments largely presume that it has been established via the delta Ct data that the gene encoding PRO1800 is *overexpressed* in the tested cell lines. The Examiner does not accept this assertion. As stated in

the previous Office action, the data show, at *best,* that the nucleic acid encoding PRO1800 is present at a level *only twice* that of the control cells. That is *not* considered to be conclusive, or even indicative that the gene is being *overexpressed.* Rather, it establishes that there are twice as many copies of the nucleic acid in the cancerous cell lines that gave a delta Ct value of greater than 1 than in the cancerous cell lines that tested negative, or the non-cancerous cells tested. A two-fold increase in nucleic acid level is more likely to be indicative of aneuploidy than it is of overexpression. The difference is key here. If the result is due to aneuploidy, then the person of ordinary skill in the art would expect that the level of PRO1800 protein, *if present at all,* would not be affected, or would be affected only in a minor fashion. Note that the result does not evidence that PRO1800 protein is being expressed in the cells *at all.* A mere measurement of the amount of nucleic acid present does not inform the person of ordinary skill in the art as to whether that nucleic acid is transcribed and translated in that cell line. The specification contains no information, assertion or data, indicating that the claimed protein was actually expressed in any of the cell lines tested. If the gene were expressed, and if it were expressed at an increased level in the cells, one would reasonably expect a greater than two-fold increase in the amount of PRO1800 nucleic acid present; each gene occurs at two copies per cell, but when it is expressed to produce protein, many more copies are made when transcription to mRNA occurs. Thus, one would reasonably expect a greater than two-fold increase if "normal" cells did not express the protein and "cancerous" cells did. The situation becomes more complex if the "normal" cells express the protein and the cancerous cells overexpress the protein. The specification provides no guidance as to whether PRO1800 protein is present in either normal or cancerous cells, and if so, at what levels. the art does not support the assertion that a two-fold increase in DNA level would be indicative of overexpression of the encoded protein. Rather, the Examiner finds that the Sen reference provides a more parsimonious explanation of the data, that the chromosome that contains the PRO1800 gene is aneuploid in some of the tested cancers.

Applicants assert at pages 17-18 of the response that "the working hypothesis among those skilled in the art is that, if a gene is amplified in cancer, the encoded protein is likely to be expressed at an elevated level." This argument has been fully considered but is not deemed persuasive because applicants have not provided any facts or evidence to support this assertion, other than the Grimaldi declaration, which is discussed below.

The declaration by Dr. Grimaldi has been fully considered but is not deemed persuasive. At paragraph 4, the declarant discusses mutations of Her2/Neu, and chromosomal translocations that are known to be associated with cancer, and states that "If the chromosomal aberration results in the aberrant expression of a mRNA and the corresponding gene product (the polypeptide) as they do in the aforementioned cases, then the gene product is a promising target for cancer therapy, for example, by the therapeutic antibody approach." This argument has been fully considered but is not deemed persuasive because it evinces that the instant specification provides a mere invitation to experiment, and not a readily available use that is enabled in a manner commensurate in scope with the claims. The PRO1800 gene, unlike Her2/Neu, has *not* been associated with tumor formation or the development of cancer, nor has it been shown to be predictive of such. Similarly, unlike t(5;14), no translocation of the chromosomal locus of PRO1800 is known to occur, nor is the chromosomal location of the PRO1800 gene known. All that the specification demonstrates is that the PRO1800 nucleic acid was amplified in 7 of 12 tested human lung tumor squamous cell cancer samples, to a minor degree, of 2-4-fold increase. No mutation or translocation of PRO1800 has been associated with lung tumor squamous cell cancer. It is not known whether PRO1800 is expressed in normal lung tissue or in lung tumor squamous cell cancer, and what the relative levels of expression are. In the absence of any of the above information, all that the specification does is present evidence that the DNA encoding PRO1800 is amplified in a small number of samples, and invite the artisan to determine the rest of the story. Such is insufficient to meet the requirements of 35 U.S.C. §112, first paragraph in a manner commensurate in scope with the claims.

At paragraph 5, Declarant argues that increased mRNA expression is expected to be associated with increased protein production. This argument has been fully considered but is not deemed persuasive because (a) this appears to be Declarant's opinion, and is not supported by fact or evidence (b) there has been no distinction on the record in general or in the specification as filed between total nucleic acid, which includes chromosomal DNA, and mRNA. One cannot determine from the data in the specification whether the observed "amplification" of nucleic acid is due to increase in chromosomal copy number, or alternatively due to an increase in transcription rates. It remains that there is no information on the record as to whether the claimed protein is expressed *at all* in lung tissue, cancerous or otherwise. It remains that, as

evidence by Pennica et al., the issue is simply not predictable, and the specification presents a mere invitation to experiment. This is further borne out by paragraph 6, which proposes further experimentation, should applicants assertions be erroneous.

At page 18, Applicant presents a declaration by Dr. Polakis filed with the response under 37 CFR 1.132. In the declaration, Dr. Polakis states that the primary focus of the Tumor Antigen Project was to identify tumor cell markers useful as targets for cancer diagnostics and therapeutics. Dr. Polakis states that approximately 200 gene transcripts were identified that are present in human tumor cells at significantly higher levels than in corresponding normal human cells. Dr. Polakis states that antibodies to approximately 30 of the tumor antigen polypeptides have been developed and used to show that approximately 80% of the samples show correlation between increased mRNA levels and changes in polypeptide levels. Dr. Polakis states that it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded polypeptide. Dr. Polakis characterizes the reports of instances where such a correlation does not exist as exceptions to the rule. This has been fully considered but is not found to be persuasive. First, it is important to note that the instant specification provides no information regarding increased mRNA levels of PRO1800 in tumor samples relevant to normal samples. Only gene amplification data was presented. Therefore, the declaration is insufficient to overcome the rejection of claims 22-29, 35 and 37-41 based upon 35 U.S.C. 112, first paragraph, since it is limited to a discussion of data regarding the correlation of mRNA levels and polypeptide levels, and not gene amplification levels and polypeptide levels. Furthermore, the declaration does not provide data such that the examiner can independently draw conclusions. Only Dr. Polakis' conclusions are provided in the declaration. There is no evidentiary support to Dr. Polakis' statement that it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded polypeptide. Finally, it is noted that the literature cautions researchers from drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue.

At page 19 of the response, applicants argue a declaration by Avi Ashkenazi. As the Ashkenazi declaration did not accompany applicants response, the Examienr will not evaluate such at this time. Applicants are reminded that each application must have a complete prosecution history in its own right.

Applicants arguments bridging pages 19-20 are not persuasive for reasons cited above. While the specification as orignally filed enables the use of PRO1800 nucleic acids or fragmen6ts thereofr for diagnosis of lung squamous cell carcinoma, there is not sufficient information in the specification as filed to indicate to one of ordinary skill in the art that it is more likely than not that the protein encoded by PRO1800 nucleic acids are diagnostic of cancer, for reasons cited above. It is further noted that while there are circumstances under which genetic markers are useful for tissue typing, such as sorting of blood cells by FACS, the mere assertion that a nucleic acid can be used for tissue typing is not considered to be a patentable utility. All mammalian genes have expression patterns; assertion that a gene/cDNA has utility because it is expressed in some cells and not others is not in and of itself a specific assertion of utility, as it can be asserted for any naturally occurring nucleic acid. It remains that while the specification is enabling of the use of SEQ ID NO: 1 or fragments thereof as hybridization probes, that enablement remains non-commensurate in scope with the claims.

Claims 22-27, 35 and 37-41 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for reasons of record in the previous Office Action.

Applicants have amended the claims to recite that the isolated nucleic acid "is overexpressed in lung or colon tumor, or wherein said isolated nucleic acid encodes a polypeptide that is overexpressed in lung or colon tumors. However, as stated in the rejection above, there is insufficient evidence of record to allow the skilled artisan to conclude that either the claimed nucleic acid or the protein it encodes are overexpressed in any tissue or cancer. The evidence of record merely indicates that PRO1800 DNA is present at elevated copy number, approximately 2-4 copies per cell, in a significant proportion of tested lung squamous cell carcinomas; there is no enablement of overexpression in that or any other cell type. With respect to lack of adequate written description, the grounds of rejection remains the same with respect to polynucleotides having at least 80%, 85%, 90%, 95% or 99% sequence identity with a particular disclosed sequence, or that merely hybridize to a disclosed sequence. The claims do not require

that the claimed polynucleotide encode a particular protein, nor that any protein encoded thereby possess any particular biological activity, nor any particular conserved structure, or other disclosed distinguishing feature. Thus, the claims are drawn to a genus of polynucleotides that are defined only by sequence identity, and now by a characteristic that has not even been established with respect to SEQ ID NO: 1. Further, even *if* SEQ ID NO: 1 were shown to be 'overexpressed' in lung or colon tumors such would not be an adequate written description of any sequence having at least 80%, 85%, 90%, 95% or 99% sequence identity with a particular disclosed sequence, or that merely hybridize to SEQ ID NO: 1 that was similarly overexpressed. There is no conception of such other sequences, merely the germ of an idea that they might exist.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, nucleic acids comprising the sequence set forth in SEQ ID NO:1, with or without the portion encoding the signal sequence, or fragments thereof sufficiently long to be used as hybridization probes but not the full breadth of the claims meet the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Applicants argument at page 21 of the response that the amendment overcomes this rejection has been fully addressed herein, and is therefore not deemed persuasive.

Rejections Over Prior Art:

The effective priority date is 5/25/2001.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 22-29, 33-35 and 37-41 remain rejected under 35 U.S.C. 102(b) as being anticipated by DE 198 18 620 (Rosenthal et al.), cited by applicants.

Rosenthal et al. disclose a nucleic acid, SEQ ID NO: 10, which is 100% identical to SEQ ID NO: 1 of the instant application, with the exception of nine nucleotides at the amino terminus of SEQ ID NO: 1. A translation of pages 1-5 and 132-133 of Rosenthal is provided, in which it is disclosed that the invention includes vectors and host cells, and fusion constructs (see pages 3-4 of translation). The person of ordinary skill in the art would recognize that numerous of the vectors listed at page 3 of the translation are specific to *E. coli*. Accordingly, the claims are anticipated.

Applicants argue at page 23 of the response that Rosenthal does not qualify as a reference under 35 U.S.C. §102(b). This argument has been fully considered but is not deemed persuasive because of the priority determination made in this case, in which priority is granted only to 5/25/2001.

Claims 22-29 and 33-35 and 37-41 are rejected under 35 U.S.C. 102(b) as being anticipated by Genbank locus AF044127, disclosed 5/27/1999. The clone is identical to nucleotides 11-terminus of SEQ ID NO: 1 of the instant application. It is disclosed as having been cloned in an M13 phage expression library, thus being an expression vector, and utilizing *E. coli* as a host cell strain. Accordingly, the claims are anticipated. Applicants argue at page 23-24 of the response that the Genbank disclosure does not qualify as a reference under 35 U.S.C. §102(b). This argument has been fully considered but is not deemed persuasive because of the priority determination made in this case, in which priority is granted only to 5/25/2001.

Advisory Information:

No claim is allowed.

Claim 32 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Lorraine M. Spector. Dr. Spector can normally be reached Monday through Friday, 9:00 A.M. to 3:00 P.M. ***Effective 1/21/2004, Dr. Spector's telephone number is 571-272-0893.***

If attempts to reach the Examiner by telephone are unsuccessful, please contact the Examiner's supervisor, Ms. Brenda Brumback, at telephone number 571-272-0961.

Certain papers related to this application may be submitted to Technology Center 1600 by facsimile transmission The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). NOTE: If Applicant does submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Official papers filed by fax should be directed to (703) 872-9306 (before final rejection) or (703)872-9307 (after final). Faxed draft or informal communications with the examiner should be directed to ***571-273-0893.***

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Lorraine Spector, Ph.D.
Primary Examiner

11/30/04